REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116 because the Amendment places the application in condition for allowance for the reasons discussed herein; and does not raise any new issues requiring further search and/or consideration. Entry of the Amendment is thus respectfully requested.

Claims 1-15 are currently pending. Claims 13-15 are canceled herein as directed to non-elected subject matter, as requested by the Examiner. Claim 1 is amended herein to remove the term "about". Thus, the present Amendment does not introduce any prohibited new matter. Applicants reserve the right to file a continuation or divisional application directed to any subject matter deleted by way of the present Amendment.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-12 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly vague and indefinite for the recitation of the term "about". Claim 1 has been amended to remove the term "about". Thus, Applicants submit this rejection is obviated.

Rejections under 35 U.S.C. § 103(a)

Applicants note with appreciation that the previous rejection of claims 1-12 under 35 U.S.C. § 103(a) over Kameyama *et al* has been withdrawn. Claims 1-12 currently stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Kameyama *et al.* (European Patent Application No. 0 378 208) in view of Gao and Wilson (U.S. Patent No.

6,281,010). Kameyama *et al.* purportedly disclose methods for the inactivation of enveloped viruses that are contaminating a protein-containing composition, by treating said compositions with 0.3% (w/v) TNP and 1% (w/v) Tween 80. Gao and Wilson purportedly disclose the medical importance of adenoviral vectors and their use in therapeutic compositions. The Office Action states that it would have been *prima facie* obvious to subject viral preparations comprising both enveloped viruses and non-enveloped adenoviruses to these treatments.

Applicants traverse the rejection and assert that a *prima facie* case of obviousness has not been adduced. The test for obviousness is (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process, ***and*** (2) whether the prior art would have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success that it would work. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Thus, there must be both motivation to combine the reference and a reasonable expectation that the combination would work. The test is ***not*** just the first prong of "what the combined teachings of the references would have suggested to those of ordinary skill in the art". The second prong of the test also must be met for a *prima facie* obviousness determination.

In the instant case, Applicants submit that there is neither a suggestion of the claimed methods nor an expectation of success that the combination would work.

Kameyama *et al.* merely disclose a method for inactivating viruses present in a protein composition. More specifically, Example 1 of Kameyama *et al.* shows treatment with 0.3% of TNBP and 1% of Tween 80 of blood-derived protein preparation contaminated with both enveloped (VSV and Sindbis) and non-enveloped (Echo) viruses. After incubation at 30°C, time course sampling was conducted to determine the residual activity of the contaminating viruses. Enveloped VSV and Sindbis viruses were inactivated after 1 hour period of time whereas the infectivity of non-enveloped Echo viruses is preserved. However, Kameyama *et al.* fail to disclose or even suggest that the claimed process could be successfully carried out to adenovirus preparations with any expectation of success. The reference fails to suggest that the recombinant adenovirus recovered after such a treatment is sufficiently infective to achieve its therapeutic effect.

Gao and Wilson do not remedy the deficiencies of Kameyama *et al.* Gao and Wilson relate to packaging cell lines for complementing E1 and E4-deleted adenoviral vectors. However, both reference fail to disclose or suggest the problem of contamination of adenoviral stocks by enveloped viruses or methods of addressing such problems. In fact, to the contrary, Gao and Wilson recommend to routine procedures to produce the viral stocks. The reference discloses that after assembly and construction, the adenovirus vectors are packaged in the EI/E4-expressing cell line and that the virion particles are harvested from the cell extract and purified by buoyant density ultracentrifugation in a CsCl gradient. Therefore, Gao and Wilson fail to disclose or suggest a method of preparing the

adenoviral vectors, which comprises a step of inactivating enveloped viruses, and thus fail to remedy the deficiencies of the primary reference.

By way of clarification, Applicants provide the following discussion. Adenoviruses and Echoviruses display very different properties in terms of stability. In addition to their acid stability, Echoviruses (of the Enterovirus family) are resistant to degradation mediated by a certain number of chemotherapeutic and chemical agents. In support, Applicants provide Chapter 21 of *Virology* (1990, 2nd Ed; ed Fields *et al.*, Raven Press). Applicants direct the attention of the Examiner to page 550 of this document, which states "Enteroviruses and the antigens associated with them are resistant to all known antibiotics and chemotherapeutic agents. Alcohol (70%), 5% Lysol, 1% quaternary ammonium compounds (Roccal) or similar laboratory disinfectants are not effective. These viruses are insensitive to ether, deoxycholate, and various detergents that destroy other viruses..." [emphasis added]. In addition, this document shows that even in inactivation conditions, some organic compounds can reverse the virus inactivation, as also stated on page 550: "Treatment with 0.3% formaldehyde, 0.1N HCl or free residual chlorine at a level of 0.3-0.5 ppm causes rapid inactivation but the presence of extraneous organic matter protects the virus from inactivation" [emphasis added]. Applicants stress that blood-derived products are complex protein preparations containing extraneous organic compounds that are susceptible to provide a stabilizing effect (*e.g.*, serum albumim), and thus protect Echo viruses from inactivation by TNBP-Tween treatment.

In fact, due to the extreme complexity of the virion architecture, adenoviruses are recognized in the art as somewhat fragile. In support, Applicants submit Huygues *et al.* (1995, Human Gene Ther., 6, 1403-1416), which states "Adenoviruses are large (diameter of approximately 80 nm) and somewhat fragile" *See* first sentence, second paragraph, page 1404.

NOT IN BASIS CLAIMED

Thus, Applicants submit that there is no suggestion in the references to even try the TNB-Tween treatment to an adenovirus preparation. In fact, the only support for the suggestion to try the TNB-Tween treatment to an adenovirus preparation comes from Applicants' specification. Even if the skilled artisan considered attempting this treatment, success would not be expected. The skilled artisan would consider that the TNB-Tween treatment would be less effective than that applied to the Echo viruses, due to the recognized fragility of the adenovirus particles. On this basis, the skilled artisan would not attempt the TNBP-Tween treatment to cause a reduction in the infectivity of the adenovirus preparation, thereby rendering the recombinant viruses unsuitable for gene therapy. The skilled artisan would not have believed that such a treatment would be effective in preserving and/or improving the infectivity of the adenoviral preparation. Therefore, there was no reasonable basis for one skilled in the art to expect success in practicing the claimed process.

In addition, Applicants submit that claimed method has an unexpected advantage with respect to the disclosure of Kameyama *et al.* The working examples of the present application have demonstrated an increase of the adenovirus titers by a factor of 3 or 4

during the inactivation process. This is due to the action of TNBP solvent on virus aggregates. This improvement in the adenovirus infectivity constitutes an unexpected benefit. Therefore, the method embraced by the present invention can be seen as pioneering efforts in the field of adenovirus-mediated gene therapy to provide for the first time safer adenoviral preparations that are free of potentially harmful enveloped viruses and that can be used routinely in clinical settings.

Thus, Applicants submit that a case of *prima facie* obviousness has not been adduced. In particular, none of the cited references teach or suggest to those of ordinary skill in the art that they should or even could carry out the claimed process, and moreover a reasonable expectation of success has not been provided by the cited references. Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Amendment and Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,
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